

## **REMARKS**

### **Formal Matters**

Claims 36-39 and 41-50 are pending after entry of the amendments set forth herein.

Claims 36-50 were examined. Claims 36-50 were rejected.

Claims 40 are canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claim. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

### **Interview Summary**

Applicants wish to express their gratitude to Examiner Helms and for the interview on June 25, 2003, with Applicants' representative James Keddie and Carol Francis. A Declaration from James Trager and two publications teaching away from the invention were discussed.

Examiner Helms agreed to withdraw the rejection upon submission of the executed Declaration and the two publications.

### **PTO 1449 form**

Applicants respectfully request that the Examiner initial and return the PTO 1449 form submitted with the Information Disclosure Statement herewith in this application, thereby indicating that the references cited therein have been reviewed and made of record.

### **The Response in General**

The claims stand rejected under 35 U.S.C. §103(a) over a combination of cited references.

The Applicants submit herewith a Declaration by James Trager, Ph.D. in support of Applicants' previously made arguments, namely that: a) there is no suggestion of a dual expression cassette vector for use in *Pichia* in any of the references, b) there is no reasonable expectation of success provided by

the references, and c) the state of the art would lead a skilled person away from combining the cited references.

The Applicants also submit herewith a two reviews on antibody expression in *Pichia*, one published before the filing date of the instant application, and the other published after the filing date of the instant application, that specifically teach away from the invention.

In view of the Trager Declaration and the two reviews, withdrawal of the rejection and allowance of the claims is respectfully requested.

To the extent a further discussion is believed necessary, the Examiner is respectfully referred to the following.

### **Rejection under 35 U.S.C. §103**

Claims 36-40 and 42-49 stand been rejected under 35 U.S.C. §103(a) as obvious over Horwitz *et al* (PNAS 85:8678-8682) in view of Cregg *et al* (Developments in Industrial Microbiology 29:33-41, 1998), The Invitrogen 1997 Catalog, Sambrook *et al* (Molecular Cloning: A Laboratory Manual, Second Edition, 1989), and Robinson *et al* (US Patent 6,204,023). Specifically, claims 36-40 and 42-49 are rejected for the asserted reason that Horwitz discloses a vector system and method for production of functional antibodies in *S. cerevisiae*, which, when combined with Cregg's *Pichia* alcohol oxidase promoter, Invitrogen's *Pichia* vector system, the general cloning methodologies of Sambrook, and the dual expression cassette vectors of Robinson, renders the claims obvious to one of skill in the art.

Claim 41 has been rejected under 35 U.S.C. §103(a) as obvious over Horwitz *et al* (PNAS 85:8678-8682) in view of the secondary references cited above, in further view of Vanderlaan *et al* (US Patent 5,429,925). Specifically, claim 41 is rejected for the asserted reason that Horwitz discloses a vector system and method for production of functional antibodies in *S. cerevisiae*, which, when combined with Cregg's *Pichia* alcohol oxidase promoter, Invitrogen's *Pichia* vector system, the general cloning methodologies of Sambrook, the methodologies for producing antibodies in yeast of Robinson, and the anti-dioxin antibody of Vanderlaan renders, the claim obvious to one of skill in the art.

These rejections are respectfully traversed.

a) The cited references provide no motivation to make and use dual expression cassettes for antibody production in *Pichia*

The Applicants respectfully submit that the cited references provide no motivation to make and use dual expression cassettes for antibody production in *Pichia*.

As discussed previously, Robinson is cited on the grounds that it is asserted to provide a key element lacking in each of the other references -- namely a dual expression cassette vector for antibody production in yeast, and the Examiner has interpreted "yeast" to mean a genus of microorganisms that encompasses *Pichia*. The Applicants respectfully disagree: the disclosure of "yeast" in Robinson cannot be extended to encompass *Pichia*.

As previously discussed, Robinson uses the terms, "yeast" and "*S. cerevisiae*" interchangeably. For example, Robinson refers to the *S. cerevisiae* gene as "the yeast invertase gene", he refers to the *S. cerevisiae*, the PGK promoter as "the yeast PGK promoter", and refers to the origin of replication of the 2-micron plasmid endogenous to *S. cerevisiae* as "the yeast origin of replication, oriY, a cis-acting sequence (REP3) from the yeast endogenous 2-micron plasmid." At no point in the disclosure does Robinson define "yeast" as anything other than *S. cerevisiae*. Furthermore, the examples provided are examples of antibody expression in *S. cerevisiae*. As such, one of skill in the art would recognize that "One preferred host is yeast" (column 15, line 39) is directed *S. cerevisiae*.

These assertions are supported in paragraphs 10-14 of the Trager declaration. Dr Trager summarizes, in paragraph 14 of his Declaration that "it is my unequivocal opinion that a Skilled Person would find no suggestion in Robinson to use a dual expression cassette vector for antibody production in *Pichia*".

Since no motivation to use a dual expression cassette vector for antibody production in *Pichia* is provided in Robinson, or, in fact, in any of the other cited references, a skilled person would not find any motivation to combine the cited references to claimed subject matter obvious.

b) Successful heterologous protein expression in *S. cerevisiae* does not predict successful heterologous protein expression in *Pichia*

The Applicants respectfully submit that the cited references cannot be combined with an reasonable expectation of success.

Dr. Trager states "As such, a Skilled Person would recognize that an example of expressing a heterologous protein, such as an antibody, in *S. cerevisiae* would have no bearing whatsoever on whether or not that same heterologous protein could be expressed in *Pichia*. Even if a reference was

cited that actually showed a working method for the expression of functional antibodies in *S. cerevisiae* using a dual expression cassette vector, it is my unequivocal opinion that a Skilled Person would have no reasonable expectation of success in practicing such a method in *Pichia*."

As such, even if one *were* to interpret the word "yeast" broadly to encompass the species *Pichia*, and even if Robinson did teach successful expression of an antibody in *S. cerevisiae* using a dual expression cassette, one of skill in the art would still not be motivated to use a dual expression cassette vector for antibody expression in *Pichia*, since, as noted by Dr. Trager, there would have been no reasonable expectation of success in practicing such a method in *Pichia*.

c) The art would lead a skilled person away from combining the cited references

The Applicants respectfully submit that the art would lead a skilled person from combining the cited references.

With specific reference to antibody expression in *Pichia*, the scientific literature would lead a Skilled Person away from combining the cited references. For example, two reviews of the scientific literature on antibody expression in *Pichia* each discourage the Skilled Person from the expression of antibodies in *Pichia* using dual expression cassette vectors. These references are submitted herewith as part of an Information Disclosure Statement.

The first of these references, Pennell (*Res Immunol.* 1998 149:599-603), states "The size of the protein to be expressed may also be limiting because to our knowledge, there are no reports of proteins greater than 117 kDa being expressed in *P. pastoris*." (emphasis added) Since antibodies are generally larger than 117 kDa, Pennell's disclosure would lead a Skilled Person away from expressing a whole antibody in *Pichia*.

The second of these references, Holliger (*Methods in Mol Biol.* 2002 178:348-357), states, in point 8 on page 351 "Because bicistronic expression works only poorly in *Pichia* (unlike *E. coli*), it is preferable to use single-chain Ab formats. Two chain Ab formats require that the two chains be cloned and transformed separately". (emphasis added). Hollinger, therefore, appears to say that single expression cassette vectors are **required** if expression of two different chains of an antibody is desired.

As such, in view of these references, especially in view of Hollinger's explicit warning against dual expression vectors for antibody in *Pichia*, a skilled person would be directly led away from combining the cited references. Applicants note that Hollinger was published after that filing date of the instant application, yet represents a review of the scientific literature spanning the period from the filing date and to 2002, and evidently without the benefit of the disclosure of the present specification.

Dr. Trager agrees, and in his opinion he summarizes by saying: "it is my unequivocal opinion that a Skilled Person, in view of the cited publications (i.e., Robinson et al, *etc.*), would not find the invention obvious because the literature and common knowledge in the field would lead them away from doing so. Given that two different reviews of the field of antibody expression in *Pichia* categorically and in no uncertainty direct away from using dual expression cassette vectors, why would a Skilled Person expect it would work?"

For the Examiner's convenience, copies of Pennell and Hollinger are enclosed herewith, as part of an IDS, and the relevant sections of the two references are underlined.

In summary, a skilled person would find no specific motivation to combine the cited publications to provide the Invention, and, in fact would be strongly led away from the invention.

The Applicants respectfully submit that the foregoing discussion adequately addresses this rejection of claims 36-40 and 42-49. Withdrawal of the rejection is respectfully requested.

As for the §103(a) rejection of claim 41, this rejection further relies on a combination of the cited references and Vanderlaan also fails to support a finding of obviousness. Vanderlaan only discloses anti-dioxin antibodies, and does nothing to cure the basic element lacking in the §103 rejection -- i.e., motivation to combine the cited references to provide for the claimed dual expression cassette vector encoding an antibody heavy and light chain, and its use in antibody production in *Pichia*. Therefore, the rejection of claim 41 under 35 U.S.C. §103(a) may also be withdrawn.

**CONCLUSION**

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCAL-269.

Respectfully submitted,  
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Enclosure: Declaration of James Trager Under 37 C.F.R. §1.132 (with Exhibits A andB)